

## Incidence of voriconazole hepatotoxicity during intravenous and oral treatment for invasive fungal infections

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**Objectives:** Absorption of oral voriconazole is good and in contrast to the intravenous (iv) formulation it can be given in patients with renal insufficiency. Furthermore, the acquisition costs are significantly lower. The aim of this study was to compare the incidence of hepatotoxicity in patients treated with the oral formulation of voriconazole with that in patients treated with the iv formulation.

**Methods:** This was a retrospective observational study. A total of 35 patients with haematological disease and an invasive fungal infection were treated with oral voriconazole during the entire regimen. We compared the incidence of hepatotoxicity with that in 11 patients treated intravenously during the first week.

**Results:** The incidence of increased liver enzymes was comparable between both groups. Voriconazole was discontinued in two patients in the oral group and one patient in the iv group because of hepatotoxicity. The incidence of liver enzyme elevations in the entire study cohort of 46 patients was higher than that previously reported in a comparable study population ( $P < 0.001$ ). However, clinically significant hepatotoxicity was infrequently observed (3/46 or 6.5%).

**Conclusions:** In 35 patients with invasive fungal infections we instituted oral voriconazole therapy from day 1 and found an incidence of hepatotoxicity comparable to 11 controls treated intravenously.

Keywords: therapy, invasive aspergillosis, haematological disease

### Introduction

Invasive aspergillosis (IA) is a life-threatening infection and is almost exclusively seen in the severely immunocompromised host. It typically occurs in patients treated for haematological malignancies (5–20% in high-risk groups) especially during prolonged neutropenia, after allogeneic stem cell transplantation and in the context of graft versus host disease.<sup>1</sup>

Recently, treatment options for IA have improved with the availability of voriconazole, a broad-spectrum triazole, with a better efficacy and safety profile than amphotericin B.<sup>2</sup> One of the most common side effects during voriconazole therapy is

an increase in liver enzyme concentrations. In clinical trials with voriconazole, the incidence of hepatotoxicity varied considerably.<sup>3</sup> This may be explained by differences in the study population (adult patients with AIDS, immunocompromised children), the indication (empirical therapy versus treatment for proven IA) or the formulation [intravenous (iv) versus oral] and dosage of voriconazole that was used.

At Erasmus University Medical Center in Rotterdam, The Netherlands, voriconazole is used for the first-line therapy of probable, proven and suspected IA, as defined previously.<sup>4</sup> Because of the excellent bioavailability (96%) and reduced costs of oral voriconazole as compared with iv voriconazole

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we decided to treat patients orally for the entire regimen and therefore without 7 day iv loading. Furthermore, iv voriconazole therapy is contraindicated in patients with renal insufficiency (creatinine clearance < 50 mL/min) because of the occurrence of accumulation of the iv vehicle (SBECD).

We registered hepatotoxicity in all patients treated with voriconazole during the first year of oral voriconazole treatment for an invasive fungal infection in our hospital and compared these data with the incidence in 11 patients treated intravenously at our institution and with the incidence reported in the literature.

### Patients and methods

#### Patients

Data of all patients with a haematological malignancy and diagnosed with a proven, probable or suspected invasive fungal infection at Erasmus MC, University Medical Center, Rotterdam, The Netherlands, who were treated with voriconazole in 2003 were collected. Patients receiving empirical therapy were excluded. Eleven patients were treated first with the standard sequential 7 day iv and then with the oral regimen.<sup>2</sup> For economical reasons the first week of iv therapy was later replaced by oral therapy. Only patients who were unable to swallow oral tablets of voriconazole (mostly due to mucositis) continued to receive the iv regimen. The dosage for oral and iv therapy was the same: two doses of 6 mg/kg of body weight on day 1, then from day 2 through 7 twice daily 4 mg/kg, followed by 200 mg twice daily. After 4 weeks and when treatment response was observed voriconazole was stopped or patients were switched to oral itraconazole for secondary prophylaxis on an individual basis.

#### Toxicity registration

Bilirubin, alkaline phosphatase (ALP), serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) concentrations were measured three times a week during voriconazole therapy and recorded as absolute values and according to the NCI Common Terminology Criteria for adverse events (CTCAE version 2.0, <http://ctep.cancer.gov>). If hepatotoxicity persisted after discontinuation of voriconazole, measurement was continued until concentrations decreased to baseline. We classified hepatotoxicity according to CTC grades (grade 0, none; grade 1, >ULN–1.5 × ULN; grade 2, >1.5 × –3.0 × ULN; grade 3, >3.0–10.0 × ULN; and grade 4, >10.0 × ULN for bilirubin, and grade 0, none; grade 1, >ULN–2.5 × ULN; grade 2, >2.5 × –5.0 × ULN; grade 3, 5.0–20.0 × ULN; and grade 4,

>20.0 × ULN for ALP, AST and ALT). Furthermore, hepatotoxicity was classified as >3 × ULN and >5 × baseline values. Also, the time taken to reach the maximum hepatotoxicity level (TOXmax) and the time needed to return to the baseline value after treatment discontinuation were determined.

#### Statistical analyses

2 × 2 contingency tables were used to compare incidences between groups. The  $\chi^2$  test and Fisher's exact test when appropriate were used with *P* value <0.05 (2-tailed) was considered significant. The Mann–Whitney *U*-test was used for the comparison of the median of groups. GraphPad Prism software v3.0 was used for the analysis (GraphPad Software Inc., San Diego, CA, USA).

### Results

A total of 46 consecutive patients were included; 40 were treated for IA (21 probable, 19 suspected) and 6 for invasive candida infection. Of the 46 patients, 11 were treated with the conventional 1 week iv regimen followed by oral therapy (iv group). The other 35 patients were treated with oral therapy only (oral group). Median baseline concentrations for the 46 patients were 14  $\mu$ mol/L for bilirubin (ULN 16  $\mu$ mol/L) and 113 U/L (ULN 119 U/L), 35 U/L (ULN 36) and 44 U/L (ULN 40), respectively, for ALP, AST and ALT. Baseline values did not differ between the 11 iv and 35 oral patients (*P* > 0.1 for all, data not shown). The median highest concentrations were 37  $\mu$ mol/L and 252, 107 and 124 U/L, respectively. The median time until the highest concentration was 4, 9, 6 and 7 days for bilirubin, ALP, AST and ALT, respectively. Table 1 compares the incidence of hepatotoxicity for the iv and oral groups and also gives the incidence as observed in study protocol 307/602 (Vfend product information, Pfizer Inc. NY, NY10017) and protocol 150/304.<sup>2,5</sup> No statistically significant difference in the incidence of hepatotoxicity was observed between the iv and oral groups. The incidence of any observed hepatotoxicity at >3 × ULN in the entire study population was significantly higher than that observed in protocol 307/602 (*P* < 0.001). Despite the high incidence of elevated liver enzymes in our study, voriconazole was discontinued due to hepatotoxicity in three patients only, one in the iv group and two in the oral group. The patient in the iv group and one in the oral group showed toxicity levels of CTC  $\geq$  grade 3 (for ALP,

**Table 1.** Hepatotoxicity of voriconazole during treatment for invasive aspergillosis

	Incidence of toxicity (%) intravenous ( <i>n</i> = 11)			Incidence of toxicity (%) oral regimen ( <i>n</i> = 35)			Protocol 307/602 <sup>a</sup>	Protocol 150/304 <sup>b</sup>
	CTC increase $\geq$ 2	>3 ULN	>5 × baseline	CTC increase $\geq$ 2	>3 ULN	>5 × baseline	>3 ULN	>3 ULN
Bilirubin ( $\mu$ mol/L)	0	36.4	0	22.2	40.0	11.4	NA	NA
ALP (IU/L)	18.2	36.4	0	19.4	22.9	5.7	16	(14.6) <sup>c</sup>
AST (IU/L)	54.5	63.6	27.3	27.8	57.1	25.7	11.7	(14.6)
ALT (IU/L)	18.2	45.5	0	50	68.6	34.3	18.9	(14.6)

NA, not available.

<sup>a</sup>Vfend product information revised March 2005 (Pfizer Inc, NY, NY 10017).

<sup>b</sup>Reference 5.

<sup>c</sup>The percentage from protocol 150/304 is put in brackets because this is the incidence of any liver enzyme elevation >3 ULN and not for ALP, AST or ALT separately.

AST and ALT). In the second patient from the oral group voriconazole was stopped at CTC grade 2 for all three parameters.

The time to TOXmax was comparable for the iv and oral groups; for bilirubin  $8.2 \pm 3$  versus  $8.8 \pm 9$  days, for ALP  $12.2 \pm 6$  versus  $10.3 \pm 9$  days, for AST  $8.6 \pm 5$  versus  $7.6 \pm 5$  days and for ALT  $7.1 \pm 6$  versus  $7.0 \pm 2.6$  days. The time needed to return to baseline was also comparable (data not shown). In a significant proportion of patients liver enzymes returned to baseline during voriconazole treatment (82%, 33%, 54% and 33% for bilirubin, ALP, AST and ALT).

Drugs that were frequently used together with voriconazole and that have the potential to interact with voriconazole through cytochrome P450 mediated metabolism are ciclosporin, prednisone, omeprazole and temazepam. Other frequently used drugs were imipenem, ciprofloxacin, vancomycin, metoclopramide, furosemide, valaciclovir and penicillin. None of these drugs was associated with an increased risk of voriconazole-associated hepatotoxicity.

## Discussion

In this study the incidence of hepatotoxicity during voriconazole therapy was higher than anticipated. It was significantly higher than the incidence observed in comparable patient populations treated for IA (protocol 150/304 and protocol 307/602, Vfend product information, March 2005, Pfizer Inc. NY, NY 10017).<sup>5</sup> Data on the incidence of elevation of individual liver enzymes (ALT, AST and ALP) for protocol 150/304 are not given in the publication nor in the vfend product information. Therefore an exact statistical comparison between this study and protocol 150/304 was not possible. However the incidence was even lower than in protocol 307/602 because the incidence of the elevation of any of the liver enzymes ALT, AST and ALP was only 14.6% (20/137) in this study. The incidence of elevation of liver enzyme concentrations in a large study on voriconazole for the treatment of persistent neutropenic fever was even lower (8.9%). However, neutropenic patients with fever despite antibiotic therapy differ from patients with invasive fungal infection in many ways. Therefore, a comparison of the incidence of hepatotoxicity in our study population with those patients is less relevant. However, in only 3 of the 46 patients we studied did voriconazole treatment need to be discontinued, suggesting that the clinical impact of this observation is small. This incidence is comparable to the seven serious hepatic adverse events in 194 patients in protocol 307/602. Several reasons may explain the observed difference in hepatotoxicity. The patient population in our hospital might not be entirely comparable to the patients in protocol 307/602. For instance, a patient population with a lower mean body weight will have higher mean serum concentrations of voriconazole, and it has been suggested that serum concentrations of voriconazole are associated with liver enzyme elevations.<sup>5,6</sup> Differences in dosing regimens may be another explanation

for the reported variability in hepatotoxicity.<sup>3</sup> In the present study, voriconazole was given at a dose of 6 mg/kg orally on day 1 with a maximum of 1000 mg, resulting in a higher oral dose on day 1 in eight patients than was used in protocol 307/602 as in this study a maximum iv dose of 800 mg was given. However, if we exclude these patients from our analysis hepatotoxicity did not change (data not shown). The higher toxicity rate in our study population may be the consequence of higher voriconazole concentrations in the liver during the first week of therapy, as gastrointestinal absorption of the higher 7 day loading dose will result in high local concentrations in the portal vein, especially during the first day.

The present study was a retrospective observational study and we used 11 concurrent patients as controls. This design has clear limitations as patients were not randomized to the iv or oral groups. Also the number of patients in the iv group was small with the consequential risk of a type-II error.

In conclusion, during treatment with voriconazole for invasive fungal infection liver enzyme elevations were more frequent than reported previously but were equally frequent in patients treated orally from day 0 as in patients treated intravenously during the first week. Future prospective randomized clinical studies are needed to confirm this observation. These studies should also compare pharmacokinetic data during the first days of iv versus oral therapy and unravel the presumed but as yet unconfirmed correlation between voriconazole serum concentrations and hepatotoxicity.

## Transparency declarations

None of the authors has a financial or other conflict of interest to declare.

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